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13. ABSTRACT (Maximum 200 Words)

From August 15, 2002 through August 14, 2003 the neuroimaging facility housing a 3T MRI unit has been operational; the MRI unit has had one upgrade in software and hardware and this has added significantly to its capabilities. The primary support staff for the fMRI facility have been hired. Several software tools for image display, analysis, registration and file conversion have been developed, expanded and refined in the same time frame. Methods for semi-automated and automated image segmentation based on an unbiased edge detection method (scale-space edge detection) have been developed to the stage of routine, bug-free use. In the future we will utilize high performance computing (parallel processing methods) to reduce the computation time from approximately 40 hours to under 10 minutes for segmentation of the whole human brain. The NeuroInformatics Center (NIC) was successful in obtaining a National Science Foundation-Major Research Instrumentation grant for over $1 million to establish a high performance computing capability for the BBMI research applications during this past year. Several ongoing research projects (described below) continue to characterize the structural and functional properties of the brain systems important in sensory, perceptual and cognitive processing.

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Introduction:

The main objectives of the research are to employ structural and functional MRI to investigate (a) the fundamental mechanisms and systems essential to perceiving, localizing and attending to specific events and stimuli in complex environments, (b) the neural systems important for motor control, sensory-motor integration and learning, (c) the processes of spatial attention and spatial 'working memory' and (d) the integration of fMRI results (having high spatial resolution) with electrophysiological data (ERPs and single cell measurements) which have high temporal resolution and the integration of fMRI data with white matter 'tractography' (diffusion tensor MRI). All of these activities are part of the Brain, Biology and Machine Initiative (BBMI) at the University of Oregon.

Body:

From August 15, 2002 through August 14, 2003 the 3T fMRI unit was utilized in a number of functional brain imaging studies. There are now 14 approved human subject protocols and four non-human subject use protocols filed with the Neuroimaging center. These include studies of language processing, mapping of the far (up to 90 degrees) peripheral visual field within human cortex, the evaluation of recovery from stroke with respect to motor functions, studies of attention and studies of affective responses to competitive game playing. We have now added capabilities for white matter tractography (using diffusion tensor imaging) to expand neuroanatomic assessments of brain plasticity and interconnections; and for magnetic resonance spectroscopy (MRS) to evaluate certain key neuromodulators central to cognitive function.

Several software tools for image display, analysis, image registration and image file conversion have been developed, expanded and refined in the same time frame. Methods for semi-automated and automated image segmentation based on an unbiased edge detection method (scale-space edge detection) have been in development and are functional tools continually being refined and now being utilized in several of the BBMI research projects. This method has been used to evaluate a drug delivery system (injectable biopolymer with an analgesic compound incorporated for timed release with high local dose at the site of the wound). An abstract based on this work has been accepted for presentation at the International Conference of the Academy of Molecular Imaging in September 2003 (see attached).

To reduce the computational time of the edge detection, a joint project with the NeuroInformatics Center (NIC) has been established. The plan is to utilize high performance computing to reduce the computation time for segmenting the whole human brain from approximately 40 hours to under 10 minutes. The NIC was successful in obtaining a National Science Foundation - Major Research Instrumentation grant for over $1 million to establish a high performance computing capability for the BBMI research applications during this past year.

The building and design of special purpose MR coils has continued in the year ending August 14, 2003. These include coils for high resolution fMRI of the human visual cortex, the construction of a special holding tank and coil system for fMRI of cuttlefish, and the initial design of a system for liquid Nitrogen cooled coils for imaging of mice brains and small fish (Zebrafish and Stickleback fish) for molecular genetics studies.

With respect to the human studies of brain systems and mechanisms, human subject diffusion tensor tractograms are provided in the appendix (Figure 1). Functional MRI data from far peripheral visual field stimulation (using a novel LED display system incorporated into goggles) have been obtained and reveal previously unknown visual cortical representations (See Figure 2). These data have been accepted for presentation at the Society for Neuroscience Annual Meeting in November 2003.

Three custom-designed RF coils have been built and tested for animal studies of auditory and visual processing. Images from the coil designed for studies in the owl are provided (See Figure 3) and initial images from mice using the 3T MRI unit are also included in the appendix (Figure 4).

Interdisciplinary research training is also a primary component of the scope of work. The fMRI facility has presented a course on fMRI for faculty and graduate students from the fall of 2003 through the spring of 2003.

Finally, as noted above, the development of automated and semi-automated edge-detection software has proceeded rapidly in the past year. The objective is to remove and/or reduce user bias and selection in the data analysis process and to provide quantitative and robust methods for image segmentation and parcellation. Also, a fully functional program for the conversion of the industry standard 'DICOM' image files (that most MRI devices generate) to other commonly used image files in data analysis programs has been accomplished.

Key Research Accomplishments:

- Demonstration of state-of-the-art human and non-human subject MRI results on a routine, day-to-day basis
- Establishment of the capability to design and fabricate purpose-built MRI (RF) coils on an 'everyday' basis; construction of several new coils including a mouse brain coil
- Development of automated and semi-automated edge-detection software and demonstrated application to analysis of drug delivery in vivo

Reportable Outcomes:

Funding Applied for: NIH and NSF grant and grant renewal applications from Drs. Neville, Dassonville, Tucker, van Donkelaar, Nunnally, Smith and Dow have been written and will be submitted for January 2004 and February 1, 2004 dates.

Research Opportunities Supported: Collaborative research into blood-brain barrier properties (Dr. Ed Neuwelt, Oregon Health Science University) has been initiated with support from this award; research opportunities with Dr. Jean Decety (University of Washington) Electrical Geodesics Inc (Dr. Jeff Eriksen) and InVivoMetrics, Inc. (Gary Tye) have also resulted from this award.

Publications: Abstracts to be presented or have been presented:
Quantitative assessment of in vivo drug delivery by edge detection and segmentation of MR images by Nunnally RL, Smith JC, Gold AJ, and Dow MW (to be presented on September 25, 2003), International Meeting of the Academy of Molecular Imaging.

Human retinotopic mapping of the far periphery by Scott, G.D., Dow, M.W. and Neville, H.J. (to be presented November 2003), Society for Neuroscience.

Differential cortical activations during syntactic and semantic processing in children aged seven to nine: An event-related fMRI study by Yamada, Y., Dow, M., and Neville, H.J. (2003), Cognitive Neuroscience Society.

Manuscripts in preparation:

MRI of the Owl (Takahashi et al)
MRI Edge Detection and Segmentation in Drug Discovery Research (Nunnally et al)
Scale-space edge detection for image segmentation (Dow et al)
Mapping of the far peripheral visual cortex (Dow et al)

Conclusions:

The facility has been fully functional for the period from August 15, 2002 through August 14, 2003. Several research protocol results have been obtained, but no study has been fully completed at this time. The 3T unit has had one major upgrade in hardware and software. This has expanded the research capabilities in the areas of white matter tractography and MRS. A novel visual stimulation system (LED transmission to eye goggles worn in the magnet) has been developed and tested; results obtained on human subjects indicate that the visual cortex extends farther than previously known.

Edge detection/image segmentation software that is highly automated and free from user bias has a number of potential scientific and medical uses as a product. Quantitative assessment of any form of image data (MRI, CT, ultrasound, x-ray, optical imaging - to name the most obvious) whether from research or medical applications has many potential applications. Rapid image segmentation and parcellation could aid in the more timely review of medical imaging data and reduce the number of errors in the 'reading' of diagnostic images. This software has potential applications for computer-aided detection in radiological diagnosis. This same software can be used for better treatment planning and assessment of treatment outcomes. Achieving a run time of minutes instead of hours will be highly beneficial both in basic research and clinical care including perhaps in real time surgical planning.

References (or meeting abstracts): see above under publications

Personnel receiving pay from the research effort

Ray Nunnally	Mark Dow
Jeanette Huston	Jolinda Smith
Chuck Theobald	Scott Watrous
Alan Younis	Darlene Schanfald
Monika Moyseowicz	Felicia Katz

APPENDIX COVER SHEET

Figure 1. Left: a single slice diffusion tensor coded image (from a full brain, multislice series). Below, left: an oblique sagittal '3D' tractogram of the entire data set. Below, right: an oblique axial '3D' tractogram of the same data set. Note the red interconnects in this image showing the interconnections of the corpus collosum. The color coding indicates the primary direction of diffusion in a scheme of right-left, up-down, and into or out of the image plane.

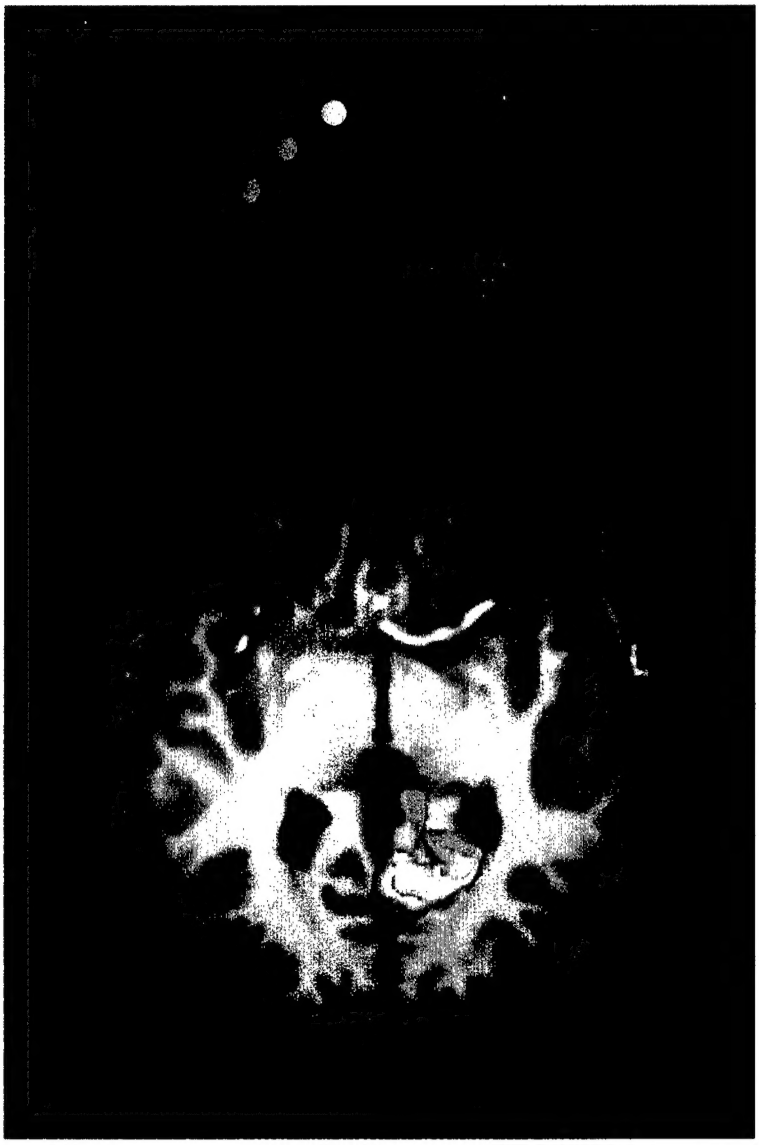
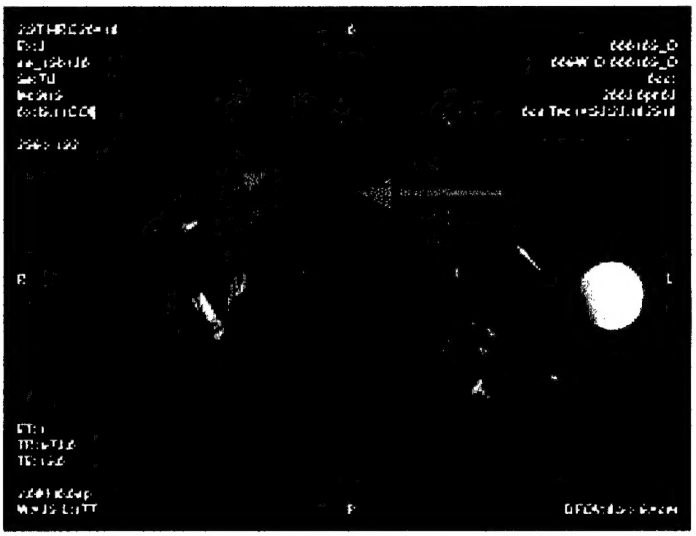


Figure 2. Color overlay of brain activation showing the position of the light stimulus in relationship to the eye and retina. The location of brain activation is color coded to the position of the light source. This is a well-established type of retinotopic mapping but has revealed heretofore unexpected extent of the visual periphery.



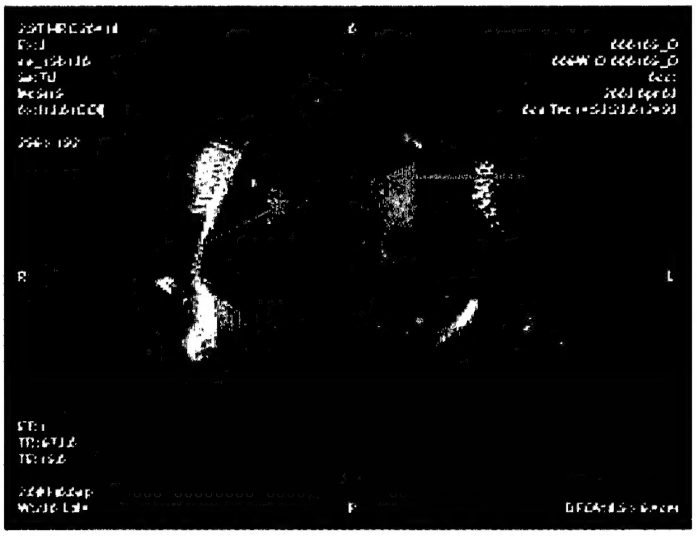
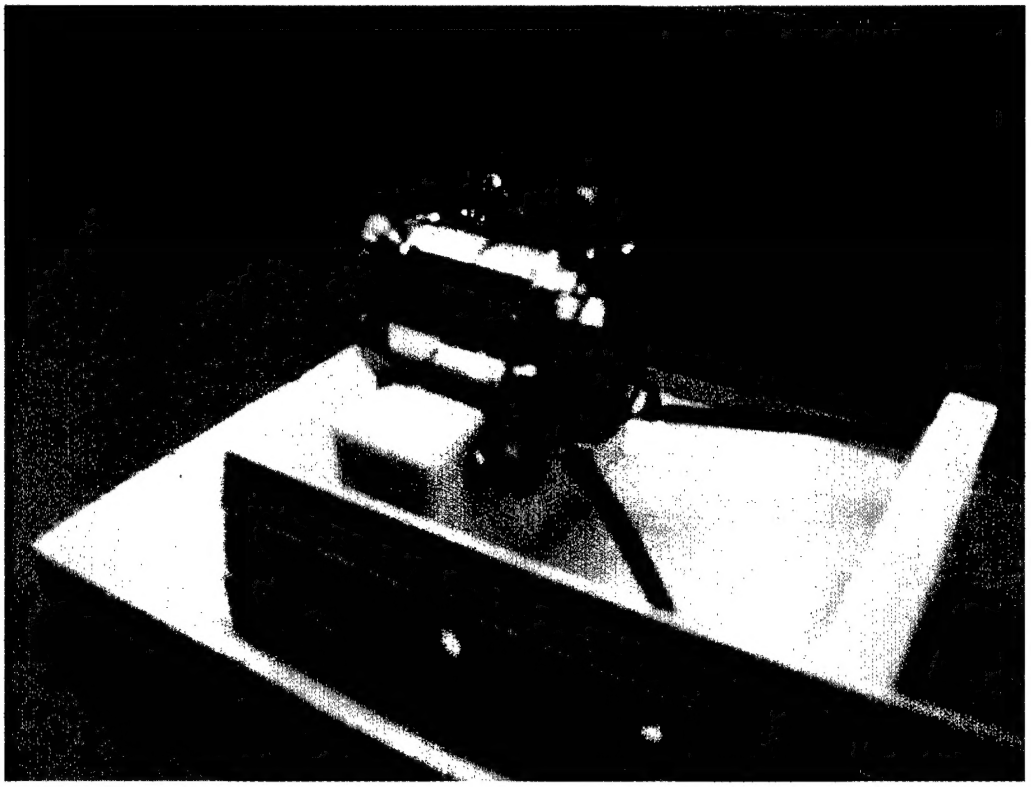


Figure 3. Two images from a live owl. The brain ( ) is well visualized as is the tract ( ) from a needle inserted into the brain and then removed. All data acquired on the 3T MRI system using s lab-built MRI coil.

Figure 4. Above: Two images form a live mouse with different contrast parameters used. Images acquired in less than 10 minutes using a lab-built 28 mm inside diameter coil.

Below: Digital photo of the mouse head coil.



Quantitative Assessment of *In Vivo* Drug Delivery by Edge Detection and Segmentation of MR Images

Introduction: Improved methods of drug delivery are an important facet of enhanced and lower-cost health care. Systems for localized, sustained drug release are an active segment of pharmaceutical research and development. Many existing FDA-cleared therapeutics can have new and extended applications if local, long-lasting release of the active drug substance is achieved. Examples of this include local sustained delivery of analgesics to surgical and trauma wound sites, local application of anti-inflammatories and sustained high-dose local administration of anti-tumor agents (e.g. Gliadel wafers, Guilford Pharmaceuticals). MR imaging is particularly well suited to the assessment of drug delivery systems *in vivo* due to its inherently high contrast-to-noise ratio (CNR) and corresponding sharp edges that occur at boundaries of signal intensity transitions.

Quantitative methods of measuring the rates of dissolution of injected or implanted polymeric drug delivery vehicles are a key to characterizing the behavior of such systems *in vivo*. Reliable results for this parameter aid in determining the compounding of the overall formulation, the volume of material administered and the frequency of re-administration. Herein is briefly described a scale-space edge detection algorithm and a semi-automated, unbiased method of image segmentation developed and implemented for application to analysis of sequential MRI data sets. We have applied these tools to the evaluation of a polymeric drug delivery system (vehicle).

Methods and Materials: The scale-space edge detection algorithm is implemented using MATLAB (Mathworks). The segmentation tool is a C++ program and runs in a Windows PC environment. Images are imported to a multi-purpose visualization and image analysis program developed in this laboratory. Segmentation utilizes a mean voxel intensity method developed by one of the authors for semi-automated image segmentation and parcellation.

Adult male rats were given bilateral, subcutaneous flank injections of ~500 uL of the viscous, non-crosslinked drug delivery system. This particular formulation does not solidify once injected. The subjects were then imaged every 12 hours over a total of 72 hours. MR images using T2 fat sat, IR and 3-D SPGR sequences were obtained at 1.5T. Two subjects were imaged simultaneously; all imaging sessions were conducted with the subjects in the supine position. Animals were anesthetized with Isoflurane and were breathing spontaneously for all sessions. The image resolution was 0.51 x 0.51 mm in-plane and slice thickness varied from 1 to 4 mm. The variously contrasted images were processed with the edge detector and segmented. The time course of the dissolution of the delivery system was determined from the segmentation volume estimates obtained from the MR scans at each time point.

Results: A typical structural T2 slice image obtained immediately post injection of the drug delivery system is shown in Figure 1a. The corresponding edge/segment overlay to the structural image is shown in Figure 1b. The areas in blue and green are the segmented regions of the vehicle in this slice. The volumes for the two regions are 445 (blue) and 470 (green) mm^3. The total volumes were obtained by adding the segmented area voxel counts from the 14 slices covering the whole extent of the vehicle.

One of the complexities of this study was the change in the T1, IR and T2 contrasts of the vehicle over time. This made the analysis of this material more difficult than what was experienced with a cross-linked polymer material that was investigated in another study.

Figure 1 (a)

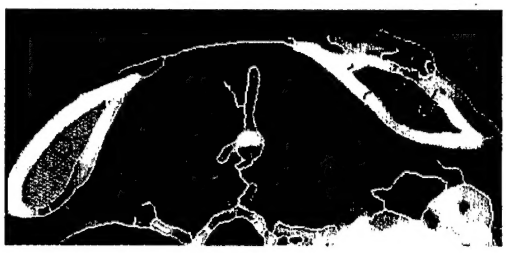


Figure 1 (b)

Conclusions: Effective quantitation of areas and volumes of drug delivery systems administered *in vivo* can be achieved by non-invasive imaging. This will aid in the development of drug delivery products at a preclinical stage and provides a direct path to designing and implementing quantitative monitoring using MRI in clinical trials and clinical follow-up for timed-release drug delivery systems.

Society for Neuroscience
New Orleans, November 2003

HUMAN RETINOTOPIC MAPPING OF THE FAR PERIPHERY

G.D. Scott; M.W. Dow; H.J. Neville*
Psychology, University of Oregon, Eugene, OR, USA

Key words: FMRI, VISUAL CORTEX

Functional MRI has been used to characterize retinotopically mapped areas of the visual cortex. Investigation of the extent of cortex used for peripheral processing has typically been limited to the central 20-30 degrees of vision (i.e.10-15 degrees eccentricity). In this study we mapped the representation of the central 140 degrees of visual field. In contrast to using the phase of BOLD response to a traveling wave of extended activity (such as a high contrast extended wedge/ring), our experiment utilized flashing spots at a limited set of visual locations. The order of the stimulation locations was random, each lasting 3 s, at an 8 Hz flash rate. While this serial excitation of small regions of cortex required more time for equivalent signal to noise at an activation site, effects of lateral inhibition were minimized. We demonstrate retinotopically organized processing in V1 and V2 out to 70 degrees visual eccentricity. In addition, some subjects show clear far peripheral retinotopy in other visual areas. The distance along the cortical surface with visual field eccentricity provides a metric of cortex used as a function of eccentricity. As in the near periphery (< 20 degrees), we find progressively less cortex involved per visual angle with increasing eccentricity.
Support Contributed By: NIH NIDCD R01DC00128

Cognitive Neuroscience Society
New York City, 2003

DIFFERENTIAL CORTICAL ACTIVATIONS DURING SYNTACTIC AND SEMANTIC PROCESSING IN CHILDREN AGED SEVEN TO NINE: AN EVENT-RELATED fMRI STUDY

Yoshiko Yamada, Mark Dow, and Helen J. Neville; University of Oregon-Eugene

Several studies have reported that in monolingual native adults syntactic and semantic processing are mediated by different brain regions. However, very little is known about when in development these different specializations arise. In this study, hemodynamic responses to syntactic and semantic/pragmatic anomalies in naturally spoken sentences were examined in children between the ages of seven and nine in an event-related functional magnetic resonance imaging (fMRI) design. Half of the sentences in the syntactic condition contained a phrase-structure rule violation, and half of the sentences in the semantic condition contained a semantically/pragmatically anomalous word. Sentences in the two conditions were intermixed. Subjects were asked to covertly make acceptability judgments after listening to each sentence. BOLD signal increase was observed within the left hemisphere for both syntactic and semantic/pragmatic conditions. Moreover, the activations were different for the two anomaly types; semantic anomalies elicited activations within the temporal lobe that were more posterior to those produced by syntactic anomalies. These results suggest that syntactic and semantic processing are mediated by non-identical neural systems in children 7-9 years of age.